Impact of allogeneic blood transfusions on clinical outcomes in severely burned patients

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Abstract: BACKGROUND: Allogeneic blood transfusions are common in the treatment of severely burned patients as surgery may lead to major blood loss. However, transfusions are associated with a number of adverse events. Therefore, the purpose of our study was to investigate the impact of allogeneic blood transfusions on clinical outcomes in severely burned patients. METHODS: This retrospective study included all adult patients admitted to the burn center of the University Hospital Zurich between January 2004 and December 2014, with burn injuries greater than 10% of total body surface area and receiving both surgical and intensive care treatment. Primary Endpoints were infectious or thromboembolic complications and mortality and secondary endpoints were length of hospital and ICU stay. Simple and multivariable logistic and linear regression models, adjusted for injury severity and confounders, were applied. RESULTS: 413 patients met inclusion criteria of which 212 patients (51%) received allogenic blood products. After adjustment for injury severity and confounders, red blood cell transfusion was independently associated with wound infection (OR 13.5, 95% CI 1.7-107, $p = 0.014$), sepsis (OR 8.3, 4.2-16.3; $p < 0.001$), pneumonia (OR 4.7, 2.2-10.0; $p < 0.001$), thrombosis (OR 3.0, 1.2-7.4; $p = 0.015$), central line infection (OR 34.7, 4.6-260; $p = 0.001$) and a longer ICU and hospital stay (difference 17.7, CI 12.1-23.4, $p < 0.001$ and 22.0, 15.8-28.2, $p < 0.001$, respectively). Fresh frozen plasma transfusion was independently associated with a longer ICU and hospital stay (difference 13.7, 95% CI 5.5-21.8, $p = 0.001$ and 13.5, 4.6-22.5, $p = 0.003$, respectively). Platelet transfusion was independently associated with systemic inflammatory response syndrome (OR 4.5, 1.3-15.5; $p = 0.018$) and mortality (OR 5.8, 2.1-16.0; $p = 0.001$). CONCLUSION: Transfusion of allogeneic blood products is associated with an increased infection rate and thromboembolic morbidity and a longer hospital stay in severely burned patients.

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Short title: Transfusions in burn patients

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Abstract

Background: Allogeneic blood transfusions are common in the treatment of severely burned patients as surgery may lead to major blood loss. However, transfusions are associated with a number of adverse events. Therefore, the purpose of our study was to investigate the impact of allogeneic blood transfusions on clinical outcomes in severely burned patients.

Methods: This retrospective study included all adult patients admitted to the burn center of the University Hospital Zurich between January 2004 and December 2014, with burn injuries greater than 10% of total body surface area and requiring both surgical and intensive care treatment. Primary Endpoints were infectious or thromboembolic complications and mortality and secondary endpoints were length of hospital and ICU stay. Simple and multivariable logistic and linear regression models, adjusted for injury severity and confounders, were applied.

Results: 413 patients met inclusion criteria of which 212 patients (51%) required allogenic blood products. After adjustment for injury severity and confounders, red blood cell transfusion was independently associated with wound infection (OR 13.5, 95% CI 1.7 to 107, p=0.014), sepsis (OR 8.3, 4.2 to 16.3; p<0.001), pneumonia (OR 4.7, 2.2 to 10.0; p<0.001), thrombosis (OR 3.0, 1.2 to 7.4; p=0.015), central line infection (OR 34.7, 4.6 to 260; p=0.001) and a longer ICU and hospital stay (difference 17.7, 95% CI 12.1 to 23.4, p<0.001 and 22.0, 15.8 to 28.2, p<0.001, respectively). Fresh frozen plasma transfusion was independently associated with a longer ICU and hospital stay (difference 13.7, 95% CI 5.5 to 21.8, p=0.001 and 13.5, 4.6 to 22.5, p=0.003, respectively). Platelet transfusion was independently associated with systemic inflammatory response syndrome (OR 4.5, 1.3 to 15.5; p=0.018) and mortality (OR 5.8, 2.1 to 16.0; p=0.001).

Conclusion: Transfusion of allogeneic blood products is associated with an increased infection rate and thromboembolic morbidity and a longer hospital stay in severely burned patients.

Key words: Burn; blood products; infections; morbidity; mortality; thromboembolic events;

Background

Transfusion and coagulation management in severely burned patients is challenging. Thermal injuries with extended soft tissue injury and subsequent inflammatory response lead to diffuse activation of coagulation factors culminating in a hypercoagulable state.[1, 2] While this alone increases the risk of developing venous thromboembolism, patients suffering from burn injuries are further exposed to numerous additional risk factors for infections, like repetitive surgical procedures, use of intravascular catheters, prolonged immobilization and multiple blood transfusions.[3, 4] Transfusions are common in burn surgery, as tangential excision may lead to major blood loss.[5] Here, apart from balanced volume replacement, hemostatic resuscitation traditionally meant early transfusion of packed red blood cells (RBC), fresh frozen plasma (FFP) and platelet concentrate (PLT) at a fixed ratio.[6, 7] However, allogenic blood transfusions are associated with a number of adverse events and it was shown that their reduction improves clinical outcomes including mortality.[4, 8] A factor-based coagulation management guided by viscoelastic point of care tests[9] has recently been proposed as a new approach of hemostatic resuscitation leading to a decreased transfusion requirement with beneficial outcomes in trauma patients.[10-13] However, burn victims are not taken specifically into account. Identification of adverse effects of allogeneic blood transfusions in severely burned patients may further promote the implementation of such goal directed coagulation management in burn patients in order to reduce transfusion requirements.[14] Therefore, the purpose of our retrospective study was to investigate the impact of allogeneic blood transfusions on clinical outcomes in severely burned patients.

Methods

Study setting and patient selection

This study was approved by the responsible ethics committee of the canton of Zurich (KEK-ZH-Nr.: 2015-111). Data handling was in accordance with the Good Clinical Practice

Guidelines and the Declaration of Helsinki for biomedical research. The study included all adult patients admitted to the burn center of the University Hospital Zurich between January 2004 and December 2014 with burn injuries greater than 10% of total body surface area (TBSA) and requiring both surgical and intensive care treatment. No substantial changes to the transfusion and coagulation algorithm were made during the observed period. To prevent a possible bias of our results we purposely terminated the observation period at the end of 2014 as in 2015 a new transfusion and coagulation algorithm was introduced at our burn center. Exclusion criteria were incomplete medical records, conservatively treated superficial burns (grade I-IIa), secondary admissions with older injuries (after the acute phase treatment in regional hospital or abroad) and all patients who received palliation-focused care because of terminal injuries. Figure 1 presents a flowchart of the patient selection.

Data collection

From the internal electronic database of the University Hospital Zurich, we extracted patient's demographics, abbreviated burn severity index (ABSI) score[15], TBSA, co-morbidities, additional injuries including inhalation injury, administered RBC, PLT and FFP transfusions, thromboembolic events, systemic inflammatory response syndrome (SIRS), sepsis, pneumonia, central line infections, urinary tract infections, wound infections, length of ICU and hospital stay as well as mortality. Additionally, we reviewed anesthesia records for administered blood products and clotting factors during all surgical procedures. Extracted data was entered into a spreadsheet (Excel, Microsoft Office 2016, Redmond, WA, United States) and scores and values were calculated. Comorbidities were summarized calculating the Charlson co-morbidity index.[16] All patients received venous thromboembolism prophylaxis with low molecular weight heparin. SIRS and sepsis were defined according to the definition consensus of the American Burn Association related to the observation period.[17] The ABSI is a model to assess accurately[15] probability of mortality, that uses age, TBSA, inhalational injury, gender

and the presence of full thickness burns to generate a score. It is therefore also used as an equivalent of burn injury severity.

Endpoints and outcome variables

The aim of our study was to analyze the impact of allogeneic blood transfusions on clinical outcomes. Primary endpoints were thromboembolic events, SIRS, sepsis, pneumonia, central line infection, urinary tract infection, wound infections and mortality. Secondary endpoints were length of ICU and hospital stay in severely burned patients.

Statistical analyses

In a first step of the analysis, we expressed distribution of variables using means and standard deviation (SD) for normally distributed continuous data, and medians and interquartile ranges (IQR) for non-normally distributed data. We tested data for normality with the Kolmogorow-Smirnow test and performed quantile-quantile plots of dependent variables. In a second step, we used simple logistic and linear regression models, followed by the main analysis, a multivariable logistic and linear regression model for the following parameters: thrombosis, SIRS, sepsis, pneumonia, central line-associated infections, urinary tract infections, wound infection, mortality, length of ICU stay and length of hospital stay. Thereby we adjusted for the following confounders known from the literature, based on the clinical experience and statistical models: ABSI-score, Charlson co-morbidity index, the presence of additional injuries and the administration of clotting factors.

For all results, we reported point estimates, 95% confidence intervals (CI) and p-values ≤ 0.05 considered significant. We performed the statistical analyses using the statistical program STATA SE (version 14, Stata Corp., College Station, Texas, United States).

Results

We retrospectively screened 810 patients admitted to the burn ICU of the University Hospital of Zurich during a 10-year period from 2004 to 2104. We then excluded 397 patients who did not meet inclusion criteria. Of the remaining 413 patients, 212 patients (51%) required allogenic blood products, while the other 201 patients (49%) did not (Figure 1).

The two groups were well balanced in size with a similar mean age. The prevalence of comorbidities was comparable with a Charlson co-morbidity index < 4 in 91.5% of patients who required transfusions and in 94.0% of patients who did not. Patients requiring allogenic blood transfusions were female in 32.5% compared to 18.9% in non-transfused patients. Further group differences were found regarding the severity of the burn injury, where patients receiving allogenic blood products had a larger burned TBSA and a higher ABSI score (6±2 vs. 8±2), as well as more inhalation or other additional injuries (Table 1). These group differences were considered as confounders in our regression model.

Among patients requiring RBC transfusions, sepsis occurred in nearly half of all patients. Other frequently observed complications were pneumonia (25%), central line infections (17%) and thrombosis (12.7%). Table 2 gives a detailed overview on the incidence of observed complications. After adjusting for confounders, RBC transfusion was independently associated with central line infections, wound infections, sepsis, pneumonia and thrombosis. Moreover, RBC transfusion was independently associated with a longer ICU and hospital stay. Unadjusted and adjusted odds ratios for each outcome are presented in Table 2. Mortality was not affected by RBC transfusions after adjustment (Table 2, Figure 2).

FFP was administered in 51 out of 413 included patients (12%). Leading complications in patients requiring FFP transfusions were sepsis (60.8%), pneumonia (33.3%) and central line infections (23.5%). Incidence of all observed complications as well as unadjusted and adjusted odds ratio for each outcome is presented in Table 3 and Figure 2. After adjustment, FFP

transfusion was independently associated with a longer ICU and hospital stay only. No significant association with other outcomes, in particular mortality, was observed (Table 3).

PLT transfusions were administered in 31 patients out of 413 included patients (7.5%). Frequently observed complications in patients requiring PLT transfusion were sepsis (74.2%), pneumonia (41.9%), thrombosis (22.6%) and central line infections (22.6%). Mortality was high in patients requiring PLT transfusion (58.1%). Table 4 presents unadjusted and adjusted odds ratios in detail. After adjustment, PLT transfusion was independently associated with SIRS and mortality, but not with sepsis or other outcomes (Table 4, Figure 2).

Discussion

Allogeneic blood transfusions are common in the treatment of severely burned patients as surgery may lead to major blood loss.[5, 18, 19] Currently, fixed ratio transfusion of RBC, PLT and FFP is still widely used and recommended for hemostatic resuscitation.[6, 7] However, transfusions may additionally lead to complications and worse clinical outcomes.[4, 8] In this study, we retrospectively analyzed the data of 413 burn patients admitted to the largest burn center in Switzerland. We calculated multiple regression models adjusting for possible confounders and found that RBC transfusion was associated with central line infections, wound infections, sepsis, pneumonia, thrombosis and a longer ICU and hospital stay; FFP transfusion was associated with a longer ICU and hospital stay and PLT transfusion was independently associated with SIRS and mortality.

Allogeneic blood transfusion is associated to several adverse effects.[4, 8] Repetitive surgeries with major blood loss and a concomitant hypercoagulability of burn patients complicates hemostatic and transfusion management.[1, 2, 7] As a result of the overwhelming response to severe thermal injury burn patients have increased levels of proinflammatory cytokines, which blunt erythropoietic response in the bone marrow.[20] The distinction between acute blood loss

anemia and anemia due to bone marrow dysfunction in burn patients is therefore an essential framework to lower the incidence of anemia and reduce transfusion requirement. For non-burned patients a multimodal treatment concept was introduced to reduce allogeneic blood transfusions. Such Patient Blood Management programs were confirmed to improve outcomes and reduce costs.[8, 21, 22] However, burn patients are not specially taken into account by such programs and physicians are still treating severely burned patients with an ample of transfusions reaching an overall transfusion rate up to 97.7%.[7, 18] The adverse effect of such an overflowing transfusion management cannot be neglected. Palmieri et al. showed that a restrictive transfusion strategy is feasible and well tolerated in burned patients.[23] Moreover, her group showed that a restrictive transfusion strategy halved the administered blood products without worsening outcomes in major burns.[24] In another prospective randomized trial of 345 patients Palmieri et al. demonstrated, that a restrictive transfusion strategy is not only well tolerated, but also beneficial by reducing length of ventilatory support and ICU stay.[25] While these trials were conducted in multiple centers in the United States, this conclusion is in line with our findings showing an increased ICU and hospital stay in patients requiring blood transfusions in a single European center. This implies a generalizability of the underlying results regarding the impact of transfusions on clinical outcomes.

Preventing infections is important in the treatment of burn patients. The burned body area is missing its natural barrier function and patients treated with allogeneic blood products are further exposed to a transfusion-related immunomodulation effect, as well as changes that may occur with old blood.[26] Moreover, a restrictive management in the antibiotic therapy should prevent the development of multi-resistant germs. These factors favor the occurrence of infections in burn patients, which eventually may lead to sepsis. Our findings reflect this fact by showing an independent association of RBC transfusion with central line infections, wound infections, pneumonia and sepsis confirming the findings of Palmieri et al.[27]

In line with our results, transfusion was detected as a possible risk factor for thrombosis in burned patients.[3, 28] Recently, an association of perioperative RBC transfusion with venous thromboembolism was confirmed in 750.937 non-burned patients undergoing surgery.[29] Burned patients additionally suffer from extended soft tissue injury and subsequent inflammatory response leading to a diffuse activation of coagulation factors, which culminates in a hypercoagulable state.[1, 2] While this alone increases the risk of developing venous thromboembolism, burn patients are further exposed to numerous additional risk factors, like the need of central lines or other intravascular catheters and prolonged immobilization.

Glance et al. showed an association of intraoperative blood transfusion with a higher risk of mortality in anemic patients undergoing noncardiac surgery.[4] But also in burn patients Palmieri et al. and Tavousi et al. found an increased mortality due to blood transfusions.[27, 30] However, in our analysis only PLT transfusion was independently associated with mortality, but not RBC or FFP transfusion. PLT transfusion is not frequently necessary in burned patients. Platelets drop below a critical threshold predominantly in acute situations such as major bleeding requiring successive massive transfusion. Therefore, we interpret the association of PLT transfusion with mortality more as an expression of a deranging situation, rather than a causation.

Limitations

This study has some limitations. Importantly it was a retrospective study and we are limited by the present methodological confines, as a retrospective analysis can only indicate a possible association and not causation. Further, as for all post-hoc studies, a power analysis would be inappropriate, however the confidence intervals of certain events in the regression model suggest an inadequate sample size. Due to overlapping transfusion requirements for different blood products, none of our patients had FFP or PLT transfusion only. This might mask the isolated effect of each blood product partly. Blood products are known to be transfused in higher

amounts in sicker patients. Thereby, any retrospective analysis about blood and outcome is challenging. Although patients requiring blood transfusions had a larger TBSA and more concomitant inhalation injuries, we are confident that our approach is sufficient to capture possible negative impact of allogenic blood products. We adjusted our analysis for the ABSI score, which was recently proven for its accuracy.[15] Additionally, with the adjustment for the Charlson co-morbidity index, the presence of additional injuries and the administration of clotting factors we eliminated other possible confounders in order to focus on the impact of transfusions on our outcomes. However, there might be some confounders for which we cannot account and correct retrospectively. Additional confounding factors known for blood products (e.g., elderly, cardiovascular comorbidities, anemia) can reasonably be excluded as this analyzed group of patients is in general a young and healthy population without comorbidities (mean age of 43-45 years). Therefore, we are convinced that our data are robust and conclusive.

Conclusion

Transfusion of allogeneic blood products is associated with an increased morbidity in severely burned patients. Our findings therefore support the approach of a restrictive transfusion strategy in severely burned patients.

Conflicts of interests:

AK, JR, KS, MA, PG, PS and JAP have no conflicts of interests to declare.

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Authors' Contributions

AK and JR did the artwork, contributed to data interpretation, drafting and critical revision of the manuscript. KS contributed to statistical analysis, data interpretation and critical revision of the manuscript. MA contributed to data collection, data interpretation and critical revision of the manuscript. DS, PG and PS contributed to data interpretation and critical revision of the manuscript. JP designed and coordinated the study, provided the data, contributed to data interpretation and critical revision of the manuscript. All authors read and approved the final manuscript.

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375 **Table 1: Patients' characteristic.**

	Patients requiring NO allogeneic blood transfusions (n=201)	**Patients requiring allogeneic blood transfusions (n=212)**
Age, years, mean (SD)	43.8 (16.3)	45.8 (17.9)
Sex female (%)	38 (18.9%)	69 (32.5%)
Charlson co-morbidity index, median (IQR) - <4 - ≥4	0 (0 – 1) 189 (94.0%) 12 (6.0%)	0 (0 – 2) 194 (91.5%) 18 (8.5%)
Burn % TBSA, median (IQR)	15 (12 – 24)	30 (18 – 41)
ABSI score, mean (SD)	6 (2)	8 (2)
3rd Burn	88 (43.8%)	163 (76.9%)
Inhalation injury	21 (10.4%)	36 (17.0%)
Additional injuries (other than inhalation injury)	3 (1.5%)	12 (5.7%)
SD = standard deviation; IQR = interquartile range;		

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377 **Table 2**: **Outcome Analysis for RBC transfusion in severely burned patients (n=413).**

	No RBC transfusions n=201	Requiring RBC transfusions n=212	unadjusted OR (95% CI)	p-value	adjusted OR (95% CI)	p-value
Thrombosis	8 (4.0%)	27 (12.7%)	3.5 (1.6 to 7.9)	p=0.002	3.0 (1.2 to 7.4)	p=0.015
SIRS	4 (2.0%)	15 (7.1%)	3.8 (1.2 to 11.5)	p=0.021	2.1 (0.6 to 7.5)	p=0.245
Sepsis	13 (6.5%)	103 (48.6%)	13.7 (7.3 to 25.5)	p<0.001	8.3 (4.2 to 16.3)	p<0.001
Pneumonia	10 (5.0%)	53 (25%)	6.4 (3.1 to 12.9)	p<0.001	4.7 (2.2 to 10.0)	p<0.001
Central line-associated infections	1 (0.5%)	36 (17.0%)	40.9 (5.6 to 301)	p<0.001	34.7 (4.6 to 260)	p=0.001
Urinary tract infections	4 (2.0%)	14 (6.6%)	3.5 (1.1 to 10.8)	p=0.030	2.6 (0.7 to 9.0)	p=0.138
Wound infection	1 (0.5%)	19 (9.0%)	19.7 (2.6 to 149)	p=0.004	13.5 (1.7 to 107)	p=0.014
Mortality	19 (9.5%)	44 (20.8%)	2.5 (1.4 to 4.5)	p=0.002	0.8 (0.4 to 1.7)	p=0.504
			unadjusted difference (95% CI)		**adjusted difference (95% CI)**	
Length of ICU stay (days)	7 (3 – 12)	28 (13.5 – 43)	26.1 (20.9 to 31.2)	p<0.001	17.7 (12.1 to 23.4)	p<0.001
Length of hospital stay (days)	15 (11 – 22)	36 (21.5 – 58)	27.9 (22.4 to 33.4)	p<0.001	22.0 (15.8 to 28.2)	p<0.001

Adjusted for the following confounders: ABSI-score, Charlson co-morbidity index, the presence of additional injuries and administration of clotting factors. All parametric results were presented as median (interquartile range). OR = odds ratio; CI = confidence interval; SIRS = Systemic Inflammatory Response Syndrome;

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379 **Table 3**: **Outcome analysis for FFP transfusions in severely burned patients (n=413).**

	No FFP transfusions n=362	**Requiring FFP transfusions n=51**	**unadjusted OR (95% CI)**	**p-value**	**adjusted OR (95% CI)**	**p-value**
Thrombosis	30 (8.3%)	5 (9.8%)	1.2 (0.4 to 3.3)	p=0.72	0.6 (0.2 – 1.6)	p=0.303
SIRS	14 (3.9%)	5 (9.8%)	2.7 (0.9 to 7.8)	p=0.068	1.9 (0.7 – 3.9)	p=0.294
Sepsis	85 (23.5%)	31 (60.8%)	5.1 (2.7 to 9.3)	p<0.001	1.6 (0.9 – 3.8)	p=0.119
Pneumonia	46 (12.7%)	17 (33.3%)	3.4 (1.8 to 6.6)	p<0.001	1.5 (0.7 – 3.0)	p=0.275
Central line-associated infections	25 (6.9%)	12 (23.5%)	4.1 (1.9 to 8.9)	p<0.001	1.7 (0.8 – 3.9)	p=0.200
Urinary tract infections	15 (4.1%)	3 (5.9%)	1.4 (0.4 to 5.2)	p=0.57	0.8 (0.2 – 3.2)	p=0.798
Wound infection	12 (3.3%)	8 (15.7%)	5.4 (2.1 to 14.0)	p<0.001	2.3 (0.8 – 6.2)	p=0.114
Mortality	48 (13.3%)	15 (29.4%)	2.7 (1.4 to 5.4)	p=0.004	2.0 (0.8 – 4.9)	p=0.143
			unadjusted difference (95% CI)		**adjusted difference (95% CI)**	
Length of ICU stay (days)	11 (6 – 25)	33 (15 – 44)	28.0 (19.8 to 36.3)	p<0.001	13.7 (5.5 – 21.8)	p=0.001
Length of hospital stay (days)	21 (13 – 35)	39 (23 – 66)	28.7 (19.8 to 37.6)	p<0.001	13.5 (4.6 – 22.5)	p=0.003

Adjusted for the following confounders: ABSI-score, Charlson co-morbidity index, the presence of additional injuries and administration of clotting factors. All parametric results were presented as median (interquartile range). OR = odds ratio; CI = confidence interval; SIRS = Systemic Inflammatory Response Syndrome;

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381 **Table 4**: **Outcome analysis for PLT transfusions in severely burned patients (n=413).**

	No PLT transfusions n=382	Requiring PLT transfusions n=31	unadjusted OR (95% CI)	p-value	adjusted OR (95% CI)	p-value
Thrombosis	28 (7.3%)	7 (22.6%)	2.4 (1.4 to 4.2)	p=0.002	1.9 (0.7 to 5.3)	p=0.212
SIRS	13 (3.4%)	6 (19.4%)	6.8 (2.4 to 19.4)	p<0.001	4.5 (1.3 to 15.5)	p=0.018
Sepsis	93 (24.3%)	23 (74.2%)	8.9 (3.8 to 20.6)	p<0.001	2.2 (0.9 to 5.5)	p=0.101
Pneumonia	50 (13.1%)	13 (41.9%)	4.8 (2.2 to 10.4)	p<0.001	1.9 (0.8 to 4.4)	p=0.158
Central line-associated infections	30 (7.9%)	7 (22.6%)	3.4 (1.4 to 8.6)	p=0.009	1.2 (0.4 to 3.4)	p=0.706
Urinary tract infections	16 (4.2%)	2 (6.5%)	1.6 (0.3 to 7.2)	p=0.56	0.9 (0.2 to 4.4)	p=0.862
Wound infection	17 (4.5%)	3 (9.7%)	2.3 (0.6 to 8.3)	p=0.20	0.6 (0.2 to 2.5)	p=0.489
Mortality	45 (11.8%)	18 (58.1%)	10.4 (4.8 to 22.6)	p<0.001	5.8 (2.1 to 16.0)	p=0.001
Adjusted for the following confounders: ABSI-score, Charlson co-morbidity index, the presence of additional injuries and administration of clotting factors. OR = odds ratio; CI = confidence interval; SIRS = Systemic Inflammatory Response Syndrome;						

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Figures

Figure 1: Flowchart of patient selection.

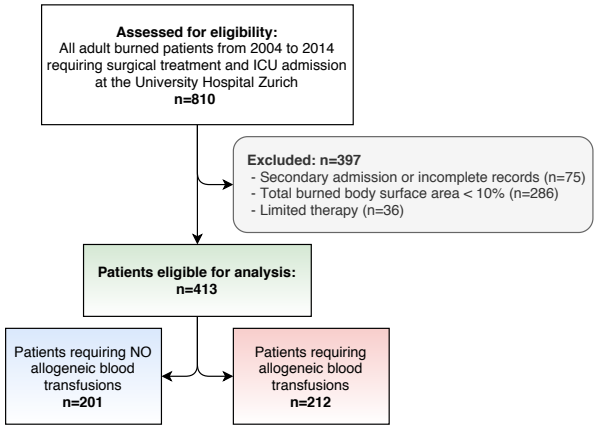

Figure 2: Odds ratios. The effect of allogeneic blood transfusion on clinical outcome in severely burned patients. Odds ratios are from the multivariate regression models adjusted for ABSI-score, Charlson co-morbidity index, presence of additional injuries and administration of clotting factors.